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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/340,690	06/29/99	NI J	1488.0770007

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EXAMINER	
KEMMERER,E	
ART UNIT	**PAPER NUMBER**
1646	16

DATE MAILED: 10/22/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/340,690	Ni et al.
Examiner	**Art Unit**
Elizabeth C. Kemmerer	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *30 Aug 2001* .

2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *27-38, 45-50, 57-62, and 81-86* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *27-38, 45-50, 57-62, and 81-86* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The reply filed 30 August 2001 (Paper No. 15) has been entered. Claims 1-26, 39-44, 51-56, 63-80 and 87-174 are canceled. Claims 27-38, 45-50 , 57-62 and 81-86 are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The objection to the amendment filed 29 June 1999 (Paper No. 3) under 35 U.S.C. § 132 regarding new matter as set forth at pp. 2-3 of the previous Office Action (Paper No. 14, 12 June 2001) is *withdrawn* in view of Applicant's convincing arguments and evidence (Paper No. 15, 09 August 2001).

The rejection of claims 27-32 and 81-86 under 35 U.S.C. § 112, first paragraph, regarding inadequate written description, as set forth at pp. 3-4 of the previous Office Action (Paper No. 14, 09 May 2001) is *withdrawn* in view of Applicant's convincing arguments and evidence (Paper No. 15, 30 August 2001).

35 U.S.C. §§ 101 and 112, First Paragraph

Claims 27-38, 45-50, 57-62 and 81-86 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. The reasons for this rejection are set forth at pp. 4-7 of the previous Office Action (Paper No. 14, 12 June 2001).

Claims 27-38, 45-50, 57-62 and 81-86 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The reasons for this rejection are set forth at p. 7 of the previous Office Action (Paper No. 14, 12 June 2001).

Applicant's arguments (pp. 6-13, Paper No. 15, 30 August 2001) have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant reviews the Utility Guidelines, and urges that the disclosure and evidence of record would be sufficient to lead one skilled in the art to conclude that the asserted utilities are more likely than not true and the examiner has not met her burden necessary to establish and maintain a rejection for lack of utility. Applicant urges that it is not a requirement of patentability to provide the logic underlying the asserted utility. Applicant argues that the homology between the claimed receptor and prior art type 2 TNF receptor indicates that the claimed TR2 has the same biological activities as type 2 TNF receptor within the legal standard of "reasonably predictive". Applicant urges that the state of the art shows that credible assertions of utility and protein function can be made based on

structural similarity, and cites three references in support of this statement. This is not found to be persuasive. As set forth in the previous Office Action, the art acknowledges that TNF receptors mediate diverse and even opposite effects. The specification also acknowledges this at pp. 73-74. In general, the art acknowledges that structural similarity among gene family members, such as growth factor, hormone or receptor families, cannot be relied upon for prediction of functional similarity. For example, Murdoch et al. (2000, Blood 95:3032-3043) reviews that chemokine receptors, which are structurally similar, are expressed on different cell types and bind different ligands such that the receptor response is highly variable (p. 3032, Abstract). Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p.

438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48). Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about

1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Applicant referred to Wilson et al., Jardins et al., and Holms at p. 11 of the response as supporting the assertion that function of a protein can be reasonably predicted from structural similarity. The findings of Wilson et al. are considered less probative than the references reviewed by the examiner above, since they concentrated on proteins that shared a secondary/tertiary structural feature (a fold) rather than on proteins that merely had high percent identity (primary structural similarity; see paragraph bridging pp. 235-236). Also, Wilson et al., admit that, for closely related sequences (such as TR2 of SEQ ID NO: 2 and the instantly claimed SEQ ID NO: 26), differences in sequence identity are more meaningful (i.e., have a greater effect on function; see p. 238). Copies of the Jardins et al. and Holms references were not submitted for independent evaluation by the examiner, and thus do not constitute convincing evidence of Applicant's position.

Applicant argues that when a class of proteins is defined such that members share a specific, substantial and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial and credible utility to the assigned protein. This is not persuasive, since such is not the case for the TNF receptor family of proteins.

Although they share structural similarity, they are known to be functionally diverse. See top of p. 74 of the specification for a review of the literature on this topic.

Applicant points to Example 6 in the specification and the Kwon et al. and Harrop et al. references as supporting the assertion that the TR2 receptors of the instant invention are capable of inducing the proliferation of lymphocytes. Applicant argues that the mere identification of a biological or pharmaceutical activity is adequate proof of practical utility, and that a biological activity has been identified for TR2, i.e., mediating human T cell proliferation. Applicant asserts that such constitutes a specific, substantial and credible utility. This is not found to be persuasive, because Example 6, Kwon et al. and Harrop et al. pertain to the activities of the receptor of SEQ ID NO: 2, not the instantly claimed SEQ ID NO: 26. As reviewed above, one cannot infer functional similarity among structurally similar TNF receptors, based on evidence in the art that the members of the TNF receptor family have diverse and even opposite activities.

Finally, Applicant urges that the examiner's discussion of alternative asserted utilities for the claimed invention in the previous Office Action is not pertinent, since only one credible, specific and substantial utility need be disclosed. Applicant asserts that the biological activity of the TR2 receptor is sufficient. However, the biological activity of the *claimed* receptor of SEQ ID NO: 26 has not been established. Thus, in the absence of an alternative asserted specific, substantial and credible utility, the claimed invention lacks any patentable utility.

Applicant urges that the rejection of the claims under 35 U.S.C. § 112, first paragraph, for lack of enablement should also be withdrawn for the reasons set forth in their arguments regarding

the rejection under 35 U.S.C. § 101 for lack of utility. This is not found to be persuasive, since the rejection under 35 U.S.C. § 101 for lack of utility is being maintained for the reasons set forth above.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D., whose telephone number is (703) 308-2673. The examiner can normally be reached on Mondays through Thursdays from 6:30 a.m. to 4:00 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached on (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ECK
October 19, 2001

ELIZABETH KEMMERER
PRIMARY EXAMINER